

What We Know About Chronic Fatigue Syndrome and Its Relevance to the Practicing Physician

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A number of recent reports have emphasized laboratory abnormalities, clinical tests, and therapeutic approaches that appear to have great promise in the evaluation and management of chronic fatigue syndrome (CFS). Because of the heterogeneity of CFS, the cost of many of these assays and procedures, and the frequent lack of skilled consultants able to apply relevant sophisticated procedures, the solo healthcare provider is often left with uncertain options in patient management. This article summarizes current approaches to patient management, utilizing available information relevant to CFS. *Am J Med.* 1998;105(3A):100S–103S. © 1998 by Excerpta Medica, Inc.

The wealth of information that is now emerging on the pathogenesis of chronic fatigue syndrome (CFS) has provided significant data regarding the pathophysiology of this debilitating disorder. As noted in epidemiologic studies, >0.5 million US citizens are likely to have typical CFS and a significantly higher proportion of the population has unexplained chronic fatigue that may share the pathogenesis of CFS. The articles included in this symposium issue discuss some of the newer insights into the biologic abnormalities associated with CFS, such as neurally mediated hypotension (NMH), hypocortisolism, possible infectious agents, and immunologic dysregulation. This article attempts to put the more significant findings in this supplement and other recent reports into a clinical perspective and to provide some guidelines as to how these findings could be utilized and considered in private practice. Because there is no current “standard of care” for CFS, it is difficult to achieve a consensus at this time, but perhaps these suggestions can be utilized as a framework for future documents.

DIAGNOSIS OF CFS

CFS has been well documented in other countries, and a number of reports from the United States and overseas have attempted to deal with the pathophysiology of this elusive syndrome, while providing guidelines to practicing physicians.^{1–8} In the United States, the latest case definition prepared by a panel convened by the Centers for Disease Control and Prevention (CDC)⁷ includes a diagnostic approach to the evaluation of patients with CFS that remains appropriate despite the numerous new laboratory findings reported in this symposium and related studies. The salient finding in all of the international studies, including those from the United States, is that there are definite laboratory abnormalities in populations of patients with CFS, although at the present time the heterogeneity of this disorder precludes any particular laboratory test being used for diagnosis. As a result, the following approach is suggested for the private practitioner.

Initial Evaluation

A presentation of prolonged fatigue is frustrating for the physician as well as for the patient. Since the first contact is likely to be a primary care physician, the first approach to evaluation should be to manage the patient with the range of skills available to the primary care physician and use consultants, such as neurologists, psychiatrists, and

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infectious disease specialists, to evaluate and manage specific symptoms that do not resolve with appropriate treatment. Recent summaries on patient management^{1,5,6,8} have emphasized that the first contact with a patient who has prolonged idiopathic fatigue is critical to the subsequent course of the disorder; hence the importance of the primary healthcare provider's taking the patient's complaints seriously, avoiding the potential harm done by an abrupt dismissal (designated "secondary wounding" by psychologists). As specific signs and symptoms indicate the need for subspecialty evaluation, appropriate referrals can be made to rule out specific neurologic, psychiatric, endocrine, and/or infectious disease processes. Psychiatric consultation may be necessary for the depression that is often concomitant, but throughout a presentation of chronic fatigue the primary physician should retain communication with the patient as other evaluations are proceeding.

As part of the initial evaluation, there are several relevant points from the epidemiologic data that need to be kept in mind. First, the case definition for CFS is a research definition, and as a result there are a number of exclusions (e.g., a history of neoplastic or other disorders) that are routinely invoked to define a more homogeneous group of patients as study subjects. Clinically, however, there is no reason why a patient excluded by a research protocol should not be managed for CFS if that is the apparent clinical diagnosis.

Second, patients presenting with fatigue who do not quite meet the case definition for CFS would still benefit from the management techniques appropriate for CFS. Assuming other diagnoses have been ruled out and the patient will continue to be monitored for an occult specific disease, the attention to symptomatic treatment and the other supportive approaches addressed in this supplement should be implemented at an early stage, well before the 6-month waiting period required by protocol for the diagnosis of CFS.

Recent studies suggest that a significant number of patients in the United States have either CFS or idiopathic chronic fatigue, and that if the symptoms persist for >1 month and remain unexplained, it is useful to enter the patient into a rehabilitation program similar to that suggested by Furst et al,⁹ even as the search for alternative explanations is in progress. Another important factor to consider is that CFS affects individuals in all socioeconomic and racial/ethnic groups and, in fact, if the same diligence is applied to evaluating various minority groups in the United States, the prevalence may even be higher than in the Caucasian non-Hispanic population.¹⁰

Laboratory Evaluation

The same basic tests suggested by Fukuda et al⁷ remain the key to diagnosis for patients being evaluated for CFS,

abnormal findings being important in detecting other disorders. Specific evidence of organ involvement—such as liver disease, cardiac abnormalities, etc.—should be evaluated independently and thoroughly. Whereas pathophysiologic aberrancies are now well documented in groups of patients with CFS, the heterogeneity of the population and the inconsistency of the observed dysfunctions appear to preclude any specific markers—particularly viral antibody levels, lymphocyte function tests, cortisol levels, and neuroimaging tests—as definitive diagnostic tools.

Future efforts in several areas (e.g., neuroendocrinology) are quite promising, however. It is now apparent that neuroendocrinology is one of the key, if not the most important, areas of research interest with clinical application at the present time. Earlier studies¹¹ have shown that low cortisol levels are a frequent finding in patients with CFS. The studies on the mechanism of hypocortisolism suggest that the defect is in the hypothalamic–pituitary–adrenal axis, and further confirmation of this was provided by the results of a placebo-controlled, double-blinded trial conducted under the auspices of the the National Institutes of Health (NIH).¹² In this investigation a therapeutic trial of hydrocortisone was shown to be somewhat effective in alleviating the symptoms of chronic fatigue, but the subsequent hypoadrenalism and the side effects of the treatment outweighed its value. Therefore, on a clinical level, attempts to control hypocortisolism appear not to be indicated.

In a similar fashion, NMH also appears to be an important part of the symptom complex in some patients with CFS, a finding that is updated in this symposium by Rowe and Calkins.¹³ Because the population seen at Johns Hopkins University may be biased (because of the tendency to refer symptomatic patients with some evidence of NMH), it is difficult to know to what extent NMH is important in the total population of CFS patients. As noted by Demitrack,¹⁴ there are a number of pitfalls in the data collected thus far, including the variability of test performance among centers. A placebo-controlled clinical trial conducted in collaboration between the Johns Hopkins University and the NIH will provide further information in this area. Meanwhile, the tilt-table test for NMH is not recommended for routine use, and the decision whether or not to evaluate a CFS patient for NMH should be based on clinical indications.

Also relevant to the neuroendocrine area are numerous studies correlating stress and changes in the endocrine and immune systems, as reviewed by the Glasers.¹⁵ This interaction, apparently important in CFS, is also believed to play a critical role in a variety of illnesses including cancer.^{16,17}

Immunology

Immune dysregulation is clearly an important component of the CFS complex. Alterations in levels and activity of circulating natural killer cells is one of the most widely found lymphocyte abnormalities in CFS patients, as summarized by Whiteside and Friberg.¹⁸ As with other tests documenting abnormalities in CFS, however, tests identifying immunologic abnormalities in CFS patients are inconsistent^{19,20} and therefore, at the present time, tests of immunologic function play no role in either the diagnosis or monitoring of patients with CFS. It is apparent that some patients with classic CFS have no identifiable immunologic abnormalities, and conversely that low natural killer cell activity and other immunologic markers can be found in a variety of situations other than CFS—and occasionally in healthy individuals. Again, as noted by the Glasers¹⁵ and Whiteside,¹⁸ immunologic dysregulation is also a frequent concomitant of stress and may be transient and unrelated to any disease process.

Neuroimaging

Neuroimaging has been widely discussed as a potential tool in documenting abnormalities of the brain in CFS, but as reviewed by Lange et al,²² there has been no substantial change since Mayberg²³ documented the pitfalls in neuroimaging interpretation and stated that in regard to CFS, magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computerized tomography (SPECT) scans remain research tools and should not be used in private practice other than to rule out other specific diagnoses.

MANAGEMENT OF CFS

The specific treatment of symptoms plays an important role in patient management, and it is imperative to address the concomitant depression, severe headache, fibromyalgia symptoms, and sleep disorders as they affect individual patients. A variety of approaches have been suggested,^{1–6,8,24} and several have been found to be effective, but individualization is necessary. As with all pharmacotherapy, patients may develop resistance to some medications, and low doses should be used initially since CFS patients are frequently extremely sensitive to pharmacologic agents.

Although at the present time there is no “magic bullet” treatment for CFS and the principles of management continue to rely on the treatment of symptoms as they arise, the continuing development of information pointing to a role of the central nervous system provides a rationale for the use of cognitive behavioral therapy, which has been shown to be effective by Sharpe²⁴ and others. The principles of cognitive behavioral therapy are closely related to the principles of rehabilitation, which is becoming an increasingly important focus of attention in CFS. The tools for the rehabilitation of the CFS patient

Table 1. Principles of Managing Patients with Chronic Fatigue Syndrome

Initial evaluation:

- Rule out other disorders beginning with recommended diagnostic tests (see *Ann Intern Med*⁷).
- Pursue specific alternative diagnoses with specialized tests and/or consultation as indicated by specific patient complaints.
- Provide strong support for patient during evaluation period, including careful attention to symptoms and emotional support (see *Gen Hosp Psychiatry*¹ and *Heart of America*⁵ for details).
- Treat specific symptoms, particularly pain, sleep disorders, and depression, realizing that low doses are often sufficient and appropriate and that different medications are effective in different patients (see *Gen Hosp Psychiatry*,¹ *J R Coll Physicians Lond*,² *Clinical Virology*,³ *Federal Practitioner*,⁴ *Heart of America*,⁵ *JAMA*,⁶ *Ann Intern Med*,⁷ and *Med J Aust*.⁸)

Management guidelines:

- Continuous support and attention to symptomatic treatment are essential.
- Proven techniques include graded monitored exercise, cognitive behavior therapy, and a number of rehabilitation approaches (See *J CFS*⁹ and *Am J Med*²⁴).
- New signs and symptoms should be evaluated as potentially new disorders and not automatically ascribed to chronic fatigue syndrome.
- The primary healthcare provider should be aware of the guidelines for social security disability,²⁶ as she/he is the most important source of relevant data in applications for disability.

are available in most rehabilitation centers, but many workers in the field do not have sufficient awareness of CFS to know how to adapt available techniques to the management of this disorder. For example, problems in word finding and other cognitive problems can be dealt with using techniques that have been applied to patients with cerebral vascular accidents,²⁵ and management of fatigue in CFS is no different than for management for fatigue in rheumatoid arthritis and multiple sclerosis.⁹

Several other important principles, discussed in more detail elsewhere and summarized in **Table 1**, should be noted. First, patients with the diagnosis of CFS should be monitored closely and new symptoms should be carefully evaluated. Not only could an underlying disorder be responsible for the fatigue emerging after a considerable latency period, but CFS patients are prone to the same infectious, neoplastic, and other severe illnesses that affect otherwise healthy individuals.

Second, care should be taken to avoid unnecessary and potentially costly and/or harmful treatments. The literature documents a number of studies attempting to show the usefulness of gamma globulin, interferon, and other agents, using the rationale that infection or immune dys-

Table 2. Attitudes Required for Effective Treatment of Patients with Chronic Fatigue Syndrome

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- Unqualified acceptance of the validity of patients' illness experience
 - Willingness to listen to their views and take them seriously
 - A positive attitude to therapy
 - Ability to tolerate slow progress and setbacks
 - Willingness to let the patient take the credit for success
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function are the major problem.³ Whereas infections are one of the stressors that may precipitate CFS, there is no evidence that infectious agents are responsible for perpetuating this disorder and, as noted above, immune dysfunction is not a consistent finding in CFS. Epstein-Barr virus (EBV) titers are specifically misused in this context, as virtually everyone in the United States is infected with EBV and, as noted by the Glaser,¹⁵ elevated antibody titers are a common finding that may or may not reflect a response to a variety of stressors.

Finally, in discussing the important qualifications of medical practitioners managing patients with CFS, Wessely et al²⁷ note five specific criteria (Table 2) that are essential to an optimal outcome for any specific patient.

In summary, CFS is clearly a treatable disorder and represents an important model for a number of illnesses requiring the basic skills of the primary healthcare provider, particularly compassion and understanding. Several techniques have proved to be effective, such as relief of specific complaints (sleep disorder, depression, pain, etc.), graded, monitored exercise, cognitive behavior therapy, and rehabilitation approaches. Other tools are on the horizon, but patience and careful monitoring are necessary to avoid the all-too-frequently used, unproved, expensive, and potentially harmful methods advocated by some.

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